Remarks

Claims 1-10 are pending in the application. Claim 4, 9, and 10 are canceled above, without prejudice, and new claims 11 and 12 are hereby added. Claim 11 finds support at, among other locations, page 5, paragraph 16, and page 13, paragraph 41, of the specification. Claims 1 and 6 have been amended above in response to the claim objections set forth at page 2 of the office action. Claims 3, 5, 6, and 7 are amended above to adjust their dependency and to replace a number of comas with semi-colons to more clearly indicate the constituents of the claimed stabilizer. Upon entry of this amendment, claims 1-3, 5-8, 11, and 12 will be pending before the Examiner.

Applicants believe that the claim objections and the §112, second paragraph, rejection set forth at page 2 of the Office Action have been obviated by the above amendments. Reconsideration is respectfully requested.

Applicants respectfully traverse the §103 rejection of claims 1 and 2 set forth at page 3 of the Office Action. In support of their traversal, Applicants note that the Chiba-ken *et al.* reference is more than 10 years old, and teaches only a vaccine comprising inactivated HAV and a stabilizing agent. The Examiner is correct that Chiba-ken *et al.* does not teach the formulation comprising live HAV. Applicants respectfully disagree with the assertions that the ordinary artisan would have been motivated to incorporate a live HAV into a formulation of Chiba-ken *et al.*, and would have had a reasonable expectation for producing the claimed invention. The present invention provides a lyophilized live hepatitis A vaccine formulation having increased thermo-stability. As mentioned in the description, one of the main disadvantages of the state of the art live attenuated vaccine is that it did not have satisfactory thermo-stability. Hepatitis A virus as well as measles virus are dissatisfactory in both storage stability and heat resistance. For example, live attentuated hepatitis A virus survives only for about 7 days at a temperature if 2-8° C, and the valid storage-term is only about 3-6 months. As a direct result, the production and transportation costs, as well as the user's expense, are extremely burdensome especially in developing countries and tropical and semitropical areas. Further, as is well known, Hepatitis A virus is a small picornavirus without outer envelope or any lipids. Like the majority of live Enteroviruses, hepatitis A virus presented in the form of aqueous suspension will rapidly lose their ability of replication or propagation, and infectious potency. Therefore, previous efforts to develop a preparation of lyophilized hepatitis A live vaccine failed. To solve this problem, the present inventors are the first to discover and teach an effective stabilizer formulation in which a live attentuated Hepatitis A virus is present. Because of the undeniable need for a stabilized live HAV vaccine formulation, and because of

the more than 10 year delay between Chiba-ken *et al.* and the priority date of the subject application (which is the first disclosure of a stabilized live HAV vaccine), it is clear that at least one of only two possibilities must be true: either the ordinary artisan was not motivated to substitute a live HAV for the inactivated HAV of Chiba-ken *et al.*; or it was attempted, but did not work. Either way, the result is the same: Chiba-ken *et al.* does not render obvious the claimed invention. To support a *prima facie* case of obviousness, one must find both the suggestion, and the reasonable expectation of success, in the prior art. Chiba-ken *et al.*, for the reasons explained above, clearly does not meet these criteria. Accordingly, Applicants respectfully request reconsideration and withdrawal of this rejection.

Next, Applicants respectfully traverse the §103 rejection over Burke *et al.* ('683) set forth at pages 3-4 of the Office Action. Although '683 mentions the word "hepatitis" amongst a long list of other viruses at column 8, line 50, it does not explicitly teach a live hepatitis vaccine, and provides no example whatsoever of a successfully stabilized lyophilized live hepatitis vaccine. As explained above, hepatitis is a picornavirus, without any lipoprotein outer envelope, which presented difficulties widely known to those of ordinary skill in the art that had, prior to the subject invention, prevented anyone from successfully producing a stabilized lyophilized hepatitis vaccine. No one knew how to protect picornaviruses that did not have lipoprotein outer envelopes, such as the hepatitis A live virus, upon lyophilization against heat inactivation prior to the subject invention. Accordingly, absent data indicating that Burke *et al.* had produced a formulation which would successfully stabilize a lyophilized live hepatitis A vaccine, one of ordinary skill in the art would not accept the offhand mention of hepatitis amongst a list of other viruses for which no data is presented as providing a reasonable expectation of successfully obtaining the stabilized lyophilized live hepatitis vaccine. Because the '683 patent does not provide a reasonable expectation of success, it cannot support an obviousness rejection. Accordingly, reconsideration and withdrawal of this rejection is respectfully requested.

Finally, Applicants respectfully traverse the §103 rejection of claims 3, 7, 9, and 10 set forth at pages 4-6 of the Office Action. Each of the rejected claims specifies a composition comprising a stabilizer for lyophilized live virus, which itself comprises either human serum albumin or gelatin, or both, amongst a plethora of other ingredients. Burke *et al.* '683 is the primary reference cited in support of the rejection of these claims, and it explicitly teaches against using gelatin as an ingredient. See, for example, column 4, lines 4-7, and column 10, lines 34-35, of the '683 patent. Accordingly, the assertion that Volkin *et al.* can be combined with the teachings of Burke *et al.* to produce a vaccine stabilizing formulation that comprises gelatin is incorrect. The teachings of cited references must be taken in their

entirety. It is thus legally improper to assert that the ordinary artisan would be motivated to combine Volkin *et al.* with Burke *et al.* None of the remaining cited references cure this problem. Accordingly, it is incorrect to assert that the prior art would have provided any motivation to the ordinary artisan to combine the references as done in this rejection. Applicants respectfully assert that the only motivation to do so is provided by the disclosure of the subject application, which recites a number of preferred embodiments whose constituents can, of course, be found in a number of different prior art documents, but such hindsight reconstruction is clearly impermissible. The motivation to combine references must be found in the prior art. Here it is not. Accordingly, reconsideration and withdrawal of this rejection is respectfully requested.

Applicants gratefully acknowledge the Examiner's indication at page 6 that claims 6 and 8 would be allowable if rewritten in independent form.

In view of the foregoing, Applicants believe that all claims currently pending are in condition for allowance, and such action is respectfully requested.

The Commissioner is hereby authorized to charge any fees under 37 CFR 1.16 or 1.17 as required by this paper to Deposit Account 19-0065.

Applicants invite the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephone interview would expedite the prosecution of the subject application to completion.

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Marked-Up Claims

1. (amended) A stabilized lyophilized hepatitis A live vaccine formulation comprising [a] prophylactically effective titers of live attentuated hepatitis A virus and a stabilizer, wherein said stabilizer is present in the vaccine formulation at a concentration sufficient to stabilize the hepatitis A virus against heat inactivation.

3. (amended) A stabilized lyophilized hepatitis A live vaccine formulation according to claim 1, wherein said stabilizer for lyophilized live hepatitis A virus comprises human serum albumin or gelatin or both of them[,]; trehalose[,]; at least one amino acid selected from the group consisting of glutamic acid, aspartic acid, arginine, lysine [or], and alkali metal salts[thereof,]of any of the foregoing; ascorbic acid[,]; urea[,]; mannitol or sorbitol or both of them[,]; and inositol.

5. (amended) A stabilized lyophilized hepatitis A live vaccine formulation according to [either one of claim 3 or 4]claim 1, wherein said stabilizer for the lyophilized live virus comprises from 0 to 20 grams per liter of human serum albumin, from 5 to 10 grams per liter of gelatin, from 50 to 100 grams per liter of trehalose, from 7.5 to 15 grams per liter of sodium glutamate, from 0.5 to 5.5 grams per liter of ascorbic acid, from 5 to 28 grams per liter of urea, from 2 to 10 grams per liter of mannitol or sorbitol, and from 4 to 10 grams per liter of inositol.

6. (amended) A method of preparing stabilized lyophilized liver hepatitis A vaccine formulation according to [any one of the claims 1 to 5]claim 1, comprising:

(a) providing a stock suspension of attentuated liver Hepatitis A virus,

(b) adding a stabilizer solution to stock suspension of attentuated live hepatitis A virus obtained from step (a) at the ratio 1:1 (v/v) to obtain a live vaccine formulation comprising prophylactically effective titers of live attentuated hepatitis A virus and a stabilizer for attentuated live virus, wherein said stabilizer comprises gelatine[, thehalose,]; trehalose; at least one [or two] amino acid selected from the group consisting of glutamic acid, aspartic acid, arginine, lysine[or], and alkali metal salts [thereof,]of any of the foregoing; ascorbic acid[,]; urea[,]; mannitol or sorbitol or a mixture of them[,]; and inositol[.]; and

(c) lyophilizing said vaccine formulation [obbtained]obtained from the step (b).

7. (amended) A stabilizer for lyophilized live virus, wherein said stabilizer comprises gelatin[,]; trehalose[,]; at least one amino acid selected from the group consisting of glutamic acid, aspartic acid, arginine, lysine [or], and alkali metal salts [thereof,] of any of the foregoing; ascorbic acid[,]; urea[,]; mannitol or sorbitol or a mixture of them[,]; and inositol.

8. (amended) A stabilizer according to claim 7, wherein said stabilizer comprises from 0 to 20 grams per [titer] liter of human serum albumin, from 5 to 10 grams per liter of gelatin, from 50 to 100 grams per liter of trehalose, from 7.5 to 15 grams per liter of sodium glutamate, from 0.5 to 5.5 grams per liter of ascorbic acid, from 5 to 28 grams per liter of urea, from 2 to 10 grams per liter of mannitol or sorbitol, and from 4 to 10 grams per liter of inositol.